(references 1 and 2) into the transformation process of Sanford et al. in order to produce a method for making localized mutations as claimed in the instant invention whereby said method can be used to correct genetic disorders in plants as suggested by Kmiec et al. (reference 2, see at least Abstract).

Applicants respectfully disagree with the Examiner's rejection.

Applicants point out that the pending claims are directed to methods for making a localized mutation causing a desired trait in a target gene in a plant cell by introducing by particle bombardment a recombinagenic oligonucleobase. The methods of the present invention allow for the site-specific change of a nucleotide in a target gene in a plant cell. Applicants note that the recombinagenic oligonucleobases of the present invention are separate and distinct from plasmids, which comprise only DNA-type nucleotides and normally contain open reading frames linked to expression control sequences and origins of replication for replication of the plasmid in one or more cell types. As explained in the specification at pages 4-7, the recombinagenic oligonucleobases, *inter alia*, have two complementary strands, in which one of the strands contains a segment of RNA-type nucleotides.

Applicants point out that Kmiec does not explicitly disclose transformation of plant cells with recombinagenic oligonucleobases using particle bombardment. Sanford teaches the transformation of cells, including plant cells, with plasmids, not recombinagenic oligonucleobases.

The Examiner's attention is invited to the Declaration of Dr. Peter R. Beetham under 37 C.F.R. § 1.132 ("the Beetham Declaration"). Dr. Beetham holds a Ph.D. and has post-doctoral experience. Dr. Beetham is at least a person of ordinary skill in the art. Dr. Beetham states his familiarity with the application and the relevant rejection. See Paragraphs 2-4 of the Beetham Declaration. Dr. Beetham explains in Paragraph 5 of his Declaration that he is a scientific investigator and manager of technical research and development, that his professional research interests have focused upon a number of areas including plant molecular biology, plant molecular virology, plant viral gene promoters, plant transformation technologies, and gene targeting in plant systems, and that he has been involved in plant tissue culture, plant genetic engineering, and more recently commercial applications for plant biotechnology. Moreover, in Paragraph 6 of the Beetham Declaration, Dr. Beetham explains that his research experience also includes the use of biolistics technology, and that more than

one thousand uses of biolistics technology in plant systems have been performed either by Dr. Beetham personally or under his supervision and control.

Dr. Beetham explains in Paragraph 7 that the biolistics technology requires the nucleic acid molecules be precipitated onto microparticle projectiles, usually a suspension of gold particles one micron in diameter, in a harsh solution of salts, *e.g.*, calcium chloride, and positively charged proteins, *e.g.*, spermadine. The nucleic acid-coated particles are then literally "shot" into cells. Dr. Beetham also explains that the application of biolistics technology to the delivery of nucleotide constructs in plants has generally been limited to double-stranded DNA plasmids typically larger than two kilobases in length, often five or more kilobases in length. Beetham Declaration, ¶ 7. Dr. Beetham states that at the time present invention was made, it was common knowledge among the scientists who were performing plant biolistics that the nucleotide constructs used in this process should be supercoiled, and that nicked and linearized structures were known to reduce efficiency. Beetham Declaration, ¶ 7. Morever, Dr. Beetham explains that fact was in accordance with the results of experiments performed by him during his doctoral studies, in which he analyzed plasmid preparations of different quality, *i.e.*, supercoiled, nicked, linear. Dr. Beetham explains that the experiment was carried out by adhering the different preparations to biolistics particles and introducing the particles into a population of plant cells. The results showed that higher quality plasmid preparations (mainly supercoiled) had higher levels of transformation than lesser quality plasmid preparations (mainly nicked and/or linear), as measured by detecting expression of a marker gene encoded by the plasmid. Beetham Declaration, ¶ 7.

Applicants note that the recombinagenic oligonucleobases of the present invention are not supercoiled. In fact, as explained by Dr. Beetham in Paragraph 8 of his Declaration:

> 8. In complete contrast, the recombinagenic oligonucleobases of the present invention are radically different in size and structure than the nucleic acid molecules that were typically employed and known to work in biolistics technology applications at the time the present invention was made. The recombinagenic oligonucleobases of the present invention are as much as two orders of magnitude smaller, and are linearized, single-stranded structures with regions of secondary structure. Moreover, the secondary structure of the oligonucleobase is required for activity. The precise mechanism by which the recombinagenic oligonucleobase molecules precipitate onto the gold particles and are subsequently resolubilized after delivery of the particles into plant cells is not well characterized.

Dr. Beetham states that it is his opinion, and believes that a scientist knowledgeable in the field of plant molecular biology and plant transformation would also hold the opinion, that the cited prior art references do not provide the required reasonable expectation of success in achieving the claimed methods because it could not have been reasonably predicted that the recombinagenic oligonucleobases could be successfully adhered to the biolistics particle and resolubilized off the particle once in the plant cell, and that it could not have been reasonably predicted that the required secondary structure of the oligonucleobase molecule would be maintained throughout the biolistics method for successfully making a desired localized mutation in a target gene. Beetham Declaration, ¶ 9.

Based on his research experience and the foregoing, Dr. Beetham concludes, and believes that a scientist knowledgeable in the field of plant molecular biology and plant transformation would also conclude, that the teachings of U.S. Patent Nos. 5,565,350; 5,731,181; and 5,204,253, either alone or in combination, do not render obvious methods of making a localized mutation causing a desired trait in a target gene in a plant cell comprising adhering to a particle a recombinagenic oligonucleobase, introducing the particle into a cell of a population of plant cells and identifying a cell of the population having a mutation, or comprising perforating the cell walls of a population of plant cells, introducing a recombinagenic oligonucleobase and identifying a cell of the population having a mutation, because the prior art does not provide a reasonable expectation of success in achieving such methods since recombinagenic oligonucleobases are sufficiently different from the double-stranded and single-stranded nucleic acid molecules employed in prior art biolistics methods. Beetham Declaration, ¶ 10. Accordingly, Dr. Beetham concludes, and believes a scientist knowledgeable in the field of plant molecular biology and plant transformation would also conclude, that the claimed methods of the present invention are nonobvious in view of the cited prior art.

A rejection for obviousness is improper when there is nothing in the cited prior art references, either singly or in combination, to suggest the desirability of the claimed subject matter. For a rejection of claimed subject matter as obvious in view of a combination of prior art references to be upheld, (1) the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or use the claimed method, as the case may be; and (2) the prior art must have revealed that in so doing, those of

ordinary skill would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Applicants point out that based on the foregoing discussion and the Declaration of Dr. Beetham there is no reasonable expectation of success that the particle bombardment method of Sanford would allow for the successful making of a localized mutation in a desired gene in a plant cell using the recombinagenic oligonucleobases described by Kmiec I and II.

In view of the foregoing discussion, Applicants submit that the rejection under Section 103 is in error since the prior art does not provide the required reasonable expectation of success in achieving the claimed methods, and respectfully request withdrawal of the Section 103 rejection.

CONCLUSION

Applicants respectfully request that the remarks of the present response be made of record in the present application. Claims 1-4 and 8-27 fully meet all statutory requirements for patentability. Withdrawal of the Examiner's rejections and action for issuance is respectfully requested.

Applicants respectfully request that the Examiner call the undersigned at (212) 790-9090 if any questions or issues remain.

Respectfully submitted,

Date: June 6, 2001

Thomas E. Friebel 29,258
Thomas E. Friebel (Reg. No.)

By: William Thomann 40,203
William Thomann (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Enclosures